REMARKS

The amendments to claim 6 find support in the application as filed, for example, at page 10, lines 20-25; page 91, lines 9-13 and 22-33; page 92, lines 22-33; and elsewhere in the application as originally filed.

No new matter is added by way of the amendments to the claims.

Applicants acknowledge with appreciation the withdrawal of the rejections under 35 U.S.C. § 112, first paragraph for enablement and for written description concerning essential material.

The Rejections of Claims 6-9 under 35 U.S.C. § 112, Second Paragraph

Claims 6-9 stand rejected as allegedly indefinite under 35 U.S.C. § 112, Second Paragraph, the USPTO wondering "how SEQ ID NO:45 could be both overexpressed and underexpressed in a sample" (page 4, lines 14-15 of the instant Office Action). Applicants respectfully traverse the rejection.

Applicants believe that the present amendments to claim 6 obviate the rejections. Claim 6 explicitly states that the claimed methods are directed to "the diagnosis of a pathological condition in a human subject characterized a) by the overexpression of a neurotrophic factor or b) by the underexpression of a neurotrophic factor" and that the diagnosis is made "if said neurotrophic factor is either a) overexpressed in said sample, or b) underexpressed in said sample..." Thus, by the clear wording in the claim, it is clear that it is **not** required that SEQ ID NO:45 be both overexpressed and underexpressed in a sample.

Accordingly, Applicants submit that the rejections of claims 6-9 under 35 U.S.C. § 112, second paragraph, are overcome.

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 6-9, and 12 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly lacking enablement for a method of diagnosis of malignancy (page 4, lines 22-23) and apparently as allegedly lacking enablement for a method of diagnosis of malignancy, tumor, abnormal growths, or pancreatic disease (page 5, lines 7-9). Applicants respectfully traverse the rejection.

The Wands Factors

Applicants submit that an analysis of the present claims in view of the factors enumerated in *In re Wands* (8 USPQ2d 1400 (Fed. Cir. 1988)) results in the conclusion that the present claims are enabled by the disclosure of the specification as filed and in view of the skill and knowledge of one of ordinary skill in the art.

Applying the *In re Wands* factors to the present claims, we find that:

1) The nature of the invention:

The claims are drawn to methods for diagnosis of pathological conditions. The claims require that the pathological conditions be either a) overexpression of a neurotrophic factor, or b) underexpression of a neurotrophic factor. The claims further require that such overexpression, or such underexpression, be considered "as compared to the expression of said neurotrophic factor measured in a sample from a normal subject." Since the overexpression and underexpression is with respect to a normal subject, determination that the neurotrophic factor is overexpressed, or, alternatively, is underexpressed, would identify a condition that would be *prima facie* pathological. Thus, the claim is indeed directed to the diagnosis of pathological conditions, as would be recognized by one of ordinary skill in the art, and is a fairly routine sort of method. For example, the claimed methods all require the same routine steps of contacting a sample and of detecting the presence of the neurotrophic factor; such steps routine laboratory or clinical operations, and are not complex since they all share the same, few steps, and thus the nature of the invention is not complex.

Moreover, the specification clearly names the particular pathological conditions to be diagnosed (see, e.g., page 91, lines 9-13), and discloses that these named pathological conditions may be diagnosed by the detection of over- or underexpression of a neurotrophin by detecting binding to a trk receptor (page 10, lines 20-25), such as a human trkB polypeptide (page 6, lines 7-32), and that the neurotrophin may be selected from BDNF, NT-3, NT-4, and NT-4/5 (page 16, lines 1-2).

2) The state of the prior art:

Although the prior art fails to anticipate the present invention, as acknowledged by the USPTO at page 6, lines 5-7, it does serve to provide an underlying basis for the enablement of the invention, since the prior art provides the requisite skills and knowledge needed to practice the claimed invention, including, in view of the teaching of the application, methods for detecting the overexpression and underexpression of one of the named neurotrophic factors. Applicants further note that, at the time the application was filed, it was well known to measure levels of a molecule of interest in normal tissue as well as in diseased tissue, and thus compare levels of that molecule of interest in control and in test tissue samples.

The USPTO is concerned that, since TrkA receptor also binds NT-4/5 (SEQ ID NO:45), and since one allegedly cannot predict whether the endogenous ligand NT-4/5 (SEQ ID NO:45) at a reduced level in pancreatic cancer is in free form or bound, one allegedly cannot predict that the administered TrkB receptor (SEQ ID NO:2) is able to compete with and displace the endogenous TrkA receptor or TrkB receptor. However, such concerns are believed to be unwarranted, as one of ordinary skill in the art would recognize that where the desired outcome is to "compete with and displace the endogenous TrkA receptor or TrkB3 receptor" as stated by the USPTO (page 7, lines 4-5 of the instant Office Action), one need only to increase the concentration of the exogenous ligand, an action that is well within the skill of one of ordinary skill in the art, in order to achieve the desired level of binding.

In addition, although the present methods are novel and not obvious over the closest prior art, which fails to teach detection of NT-4 using human trkB receptor, Applicants note that the cited reference, Schneider et al., demonstrates that one can detect a malignancy, such as pancreatic cancer, by detecting the underexpression of NT-4. Thus, the state of the prior art is supportive of enablement of the present invention.

3) The relative skill of those in the art:

Applicants reiterate that the relative skill of those in the art is high. Even were the suggestion by the USPTO that "one cannot predict that the claimed neurotrophic factor is over- or underexpressed in a pathological condition" (page 7, lines 17-19 of the instant Office Action)

to be correct, the fact remains that those of ordinary skill in the art are typically scientists with advanced degrees, or medical practitioners with advanced medial training and clinical experience. Such persons have a high level of skill.

Thus, in view of the high level of skill in the art, Applicants submit that no undue amount of experimentation would be required to practice the invention since detection of labeled polypeptides is well-known and routine in the art, well within the skill level of one of ordinary skill in the art; since the specification provides detailed explanation and examples related to the claimed methods (see, e.g., pages 79-81; 86-90, particularly 86-87; and elsewhere in the application); and since it would be a matter of routine to measure over- or underexpression of a neurotrophic factor selected from the group consisting of NT-4 and NT-4/5 by measuring their binding to labeled human trkB receptor polypeptide.

4) The predictability or unpredictability of the art:

The USPTO suggests that "which pathological conditions, which malignancy, which tumor or which pancreatic disease under- or over-expresses the claimed neurotrophic factor, or NT-4 or NT-4/5 is not predictable" and cites certain scientific articles to suggest that trkA, trkB, and trkC may be expressed differently in different diseases (pages 8-9, instant Office action). However, Applicants have discovered, and disclosed, the present methods for measuring neurotrophic factor levels and for using such levels in diagnostic methods. Furthermore,. analogous techniques are also known in the art and are predictable; the application discloses the particular and novel aspects of the claimed methods, which are also predictable in that they rely on the disclosed sequences and are also based on methods and skills that are well-known in the art. In addition, the application as filed explicitly discloses the pathological conditions to which the claimed diagnostic methods are directed; thus, Applicants submit that the predictability of the art related to such diagnostic methods is quite high.

The USPTO cites Soontorniniyooomkij et al. and Guate et al. as suggesting that the level of expression of a protein in a disease is unpredictable. Applicants note that these references, directed to measurements of levels of neurotrophins and/or neurotrophin receptors, demonstrate

that one of ordinary skill in the art would be able to practice and use the claimed methods, since these references discuss neurotrophin levels, using different methods, but showing that such measurements were possible and known to be of scientific and diagnostic value at the time of the invention. In view of the teaching in the application (e.g., Examples 1-6, pages 94-116) one of ordinary skill in the art could use such skills (as evidenced, e.g., by Soontorniniyooomkij et al. and Guate et al.), to practice the invention as taught in the present application.

The USPTO also suggests that the claimed probe, trkB receptor, "would be non-specific" and allegedly would bind other neurotrophic factors, and so one allegedly "cannot predict that the level of the specific NT-4/5 (SEQ ID NO:45) would not be interfered by the presence of other NT factors" (page 9, lines 19-21 of the instant Office Action).

Applicants do note that the specification provides data for BDNF and NT-3 binding to trkB; thus, BDNF and NT-3 may bind to the trkB receptor. However, even if other ligands bind the human trkB receptor polypeptide, or an immunoadhesin thereof, such binding may be diagnostic of a pathological condition.

With respect to the USPTO's concerns regarding whether or not the claimed trkB polypeptides are suitable probes for pancreatic cancer (pages 9-10 of the instant Office Action), Applicants note that the present claims do not require the presence of endogenous trkB receptors, and, as discussed above, one of ordinary skill in the art would recognize the possibility of increasing trkB receptor concentration if evidence of binding competition were to be observed.

5) The breadth of the claims:

The USPTO suggests that the claims are broad (page 10, lines 15-19 of the instant Office Action), noting that they encompass numerous possible pathological conditions. However, the claims are narrowly drawn to methods requiring detecting binding to human trkB receptor polypeptide comprising sequence SEQ ID NO:2 or SEQ ID NO:4. The methods steps are limited to steps using these defined molecules; the fact that these steps invented by the present inventors are suitable for the diagnosis of numerous conditions does not mean that the claimed methods are overly broad, but merely that the narrow, focused methods of the claims has significant applicability. The fact that such applicability includes applicability to the named

particular manifestations, such as a malignancy (claim 7), or a tumor (claim 8), or a pancreatic disorder (claim 9), does not increase the breadth of the claim, as all the claims are limited to methods related to disorders with the named characteristic (over- or underexpression of a neurotrophic factor). Thus, the claims are not broad in that the claimed subject matter is explicitly recited in the claims and limited to particular pathological conditions all exhibiting the named identifying characteristic.

6) The amount of direction and absence of working example

The USPTO acknowledges that the specification and the art disclose how to measure the level of the neurotrophin factor (page 1, lines 12-13 of the instant Office Action), but suggests that undue experimentation would be required to practice the claimed invention. The USPTO suggests that the specification does not disclose which diseased tissue or which disease under- or overexpresses the claimed neurotrophic factor (page 11, lines 13-15 of the instant Office Action). However, the application discloses and teaches methods for measuring neurotrophin levels in tissue, which can be normal or diseased tissue. Applicants submit that the application provides sufficient guidance and direction as to enable one of ordinary skill in the art to practice the invention without undue experimentation.

Thus, the application discloses comparison of normal and diseased state in the application as originally filed, and teaching methods for measuring neurorophin levels in tissue, which can be normal or diseased tissue. Accordingly, in view of such teaching, and in view of the analysis of the *In re Wands* factors indicating that the amount of experimentation required to practice the invention is not undue, Applicants submit that the claims are enabled and that the rejections of claims 6-9, and 12 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement are overcome.

CONCLUSION

Applicants respectfully request consideration and allowance of claims 6-9 and 12 as amended. In view of the allowable subject matter of the linking claim, claim 6, Applicants further request that the restriction requirement be withdrawn and that the remaining, withdrawn claims and subject matter be examined and allowed. Early notification of the allowance of the application is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Although no fees are believed to be due, please charge any fees due, including any fees for extension of time and for any other fees due, to Deposit Account No. **08-1641** (**Attorney's Docket No. 39766-0033 CP2C2C1**).

Respectfully Submitted,

Date: December 20, 2007

By: _____
James A. Fox (Reg. No. 38,455)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park , California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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